Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Resnic FS, Majithia A, Marinac-Dabic D, et al. Registry-based prospective, active surveillance of medical-device safety. N Engl J Med. DOI: 10.1056/NEJMoa1516333

Supplemental Appendix: Prospective Active Medical Device Safety Surveillance

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A. Investigators:

The authors are listed in the order of their relative contribution to the task noted.

1. **Study Design**: Resnic, Matheny, Robbins, Marinac-Dabic and Normand
2. **Data Collection**: All data was collected via the NCDR CathPCI Registry database. Ponirakis and Hewitt were responsible for the upload of the de-identified "limited" CathPCI dataset onto the secure DELTA server.
3. **Data Analysis:** Matheny, Resnic, Robbins, Majithia and Ssemaganda
4. **Manuscript Authors:** Resnic, Majithia, Robbins, and Matheny
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6. **Critical Edits and Review of Manuscript:** Normand, Marinac-Dabic, Loyo-Berrios, Hewitt, Ponirakis, Moussa, and Drozda.
7. **First Draft Authors:** Resnic and Majithia

B. Supplemental Appendix Methods

B.1.a Description of the Data Extraction and Longitudinal Trend Analysis (DELTA) Surveillance System: The DELTA system is a collection of integrated computer applications capable of linking to multiple databases used to capture patient characteristics, exposures to medical devices and medications and the outcomes to treatments through read-only access to the underlying data-source. DELTA has been in development since 2005 and has been implemented in prospective clinical data collection environments since 2009. The tool uses a web-based graphical user interface developed in Microsoft .NET (Microsoft, Redmond, WA), and stores data and algorithms in a SQL 2005 server. (Microsoft, Redmond, WA). DELTA allows the user to specify a desired confidence interval to generate an alerting threshold, and to select the time interval for analysis. When the application detects an elevated outcome rate for a given exposure, alerts are generated and emailed to the designated researcher. DELTA incorporates a variety of frequentist and Bayesian methods to perform risk-adjusted prospective surveillance analyses, including survival studies, sequential analyses and extensive propensity matching algorithms. DELTA uses a modular approach to statistical analysis that facilitates further expansion. DELTA can support a number of prospective safety analyses simultaneously and incorporates sophisticated security and de-identification algorithms to protect sensitive health details and uphold legislation regarding data ownership. An open-source version of DELTA is expected to be available for academic and public health use by September, 2016.

B.1.b Study Protocol and Interim Reviews: A written study protocol was adopted by the study steering committee in May, 2012, and was submitted for IRB review at both Brigham and Women's Hospital (original analytic center) and subsequently at Lahey Hospital & Medical Center. The written protocol is available at NEJM.org. The protocol details the composition and responsibilities of the scientific (study) steering committee, as well as the selection of specific devices to be studied. In addition it defines the outcomes of interest, the analytic approach (propensity matching), number of interim analyses (two followed by a final analysis), time frame for outcome ascertainment (through time of death or discharge from the treating hospital), and basis for generating DELTA safety alerts. Pre-specified sensitivity analyses included alternative event rate estimation (using logistic regression risk adjustment), and analysis of high risk subsets of patients (diabetics, age≥70 years and women) were also documented. For the purposes of this study, all such analyses are designated as "protocol pre-specified" analyses.

The protocol specified that there would be two interim reviews and a final data analysis. Following the second interim review the Scientific Steering Committee recommended the performance of additional, post-hoc, sensitivity analysis to exclude center-level confounding and potential impact of alternative approaches to handling missing data. Following the final analysis review, the Steering Committee, at the request of FDA, developed a protocol amendment to undertake a "Signal Persistence" analysis, repeating the primary analysis and high-risk subset analyses in an independent, and contemporary, dataset from CathPCI procedures performed in 2014 through 2015. This additional protocol amendment is available at NEJM.org.

B.1.c Why Study the Safety of Vascular Closure Devices? Vascular closure devices have been available since 1996 in the United States for use following PCI procedures. These devices utilize varying mechanical, pharmacologic and biomaterial components to help accelerate hemostasis by sealing or opposing the arteriotomy required to perform coronary angiography and interventional procedures. The

VCD marketed in the U.S. have generally been approved based on studies with small numbers of patients, with the primary endpoints focused on time to hemostasis and time to ambulation as compared with manual or mechanical vascular compression. In general, patient comfort is increased with the use of VCD relative to vascular compression, but they have not been definitely shown to be advantageous to compression in rates of post-procedural bleeding or other complications. Most importantly for the present study, is that there is very limited data on the comparative performance of these widely used devices.

B.2 Adverse Outcome Definitions:

All covariates and adverse clinical events were defined according to the CathPCI Registry version 4.x data definitions (available at: http://cvquality.acc.org/~/media/QII/NCDR/Data%20Collection%20Forms/cathpci_v4_codersdictionary_4-4.ashx). The specific adverse outcomes use in this study included:

Any Vascular Complication denotes the composite of bleeding at access site, hematoma at access site, retroperitoneal bleeding, and other vascular complications requiring treatment.

Bleeding at access site denotes that the patient experienced significant external bleeding that occurred at the access or percutaneous entry site. To qualify, the bleed must be associated with any of the following: 1) hematocrit drop >=10% and/or hemoglobin drop of >= 3g/dL 2) transfusion of whole blood or packed red blood cells 3) procedural intervention/surgery at the bleeding site to reverse/stop or correct the bleeding (such as surgical closures/exploration of the arteriotomy site, or balloon angioplasty to seal an arterial tear).

Hematoma at access site denotes the patient has experienced a hematoma at the percutaneous entry site. To qualify, the bleed must be associated with any of the following: 1) hematocrit drop >=10% and/or hemoglobin drop of >= 3g/dL 2) transfusion of whole blood or packed red blood cells 3) procedural intervention/surgery at the bleeding site to reverse/stop or correct the bleeding (such as surgical closures/exploration of the arteriotomy site, or balloon angioplasty to seal an arterial tear).

Retroperitoneal bleeding indicates the patient has experience a retroperitoneal bleed. CathPCI Registry v4.x does not specify how retroperitoneal bleeding (RPH) is diagnosed. Since the CathPCI Registry collects all PCI cases from over 95% of all U.S. centers performing PCI, the diagnosis of RPH is likely variable, but, by definition, is the current standard for diagnosing this condition. In all centers that the authors are familiar with, only CT scans of the abdomen and pelvis, angiographic evidence of active bleeding or direct surgical exploration are used to definitely diagnose RPH. .As with "access site hematoma", the documentation of an RPH requires additional clinical significance to be coded in the CathPCI Registry. In addition to the anatomical confirmation of RPH, the bleed must be associated with at least one of the following 1) hematocrit drop >=10% and/or hemoglobin drop of >= 3g/dL 2) transfusion of whole blood or packed red blood cells 3) procedural intervention/surgery at the bleeding site to reverse/stop or correct the bleeding (such as surgical closures/exploration of the arteriotomy site, or balloon angioplasty to seal an arterial tear).

Other vascular complications requiring treatment could include, but were not limited to, access site occlusions, peripheral embolizations, dissections, pseudoaneurysms and/or AV fistulas. Any noted vascular complication must have had an intervention such as a fibrin injection, angioplasty, or surgical repair to qualify. Prolonged pressure did not qualify as an intervention, but ultrasonic guided compression after making a diagnosis of pseudoaneurysm did qualify. A retroperitoneal bleed or hematoma requiring transfusion is not a vascular complication under this data element.

Transfusion indicated that there was a transfusion(s) of either whole blood or packed red blood cells post- procedure.

B.3. Additional Details on Methods Utilized in CathPCI DELTA Study:

Several methodological details were not explicitly specified in the original protocol but were required prior to initiation of the analysis within DELTA and are described in detail below.

B.3.a: Exclusion criteria: Based on prior clinical research on VCD performance, the steering committee chose to exclude all patients who received more than one VCD, those patients who had any non-femoral access, those patients who had multiple sites of access and those patients who received large caliber intravascular devices such as intra-aortic balloon pumps or ventricular support device as part of the PCI procedure. These exclusions were made in an attempt to isolate those patients exposed to a single active VCD, who would have been potential candidates to receive any other active VCD.

B3.b: Variable selection criteria for propensity match model: The initial covariate selection was based on prior publications related to comparative safety of VCD using propensity matching.[1] These variables were selected from among the CathPCI Registry data elements if had previously been demonstrated in published studies to be associated with any of the vascular outcomes (including access site injury, bleeding or need for post-procedural transfusion) and the covariate would have been available to the treating physician before the deployment of the VCD. Additional covariates were considered if they were thought to be related to the physician decision to choose one VCD versus another and also related to the outcome. A total of 36 covariates from among the CathPCI Registry pre- and intra-procedure data elements were considered as candidate variables for inclusion in the model.

All candidate covariates were then assessed through a data validation step within DELTA using data from the calendar quarter prior to the start of the monitoring period. To guard against the possibility of the model being unable to converge due to quasi-complete (or complete) separation, we calculated the linear Variance Inflation Factor (VIF) for each candidate covariate excluding from the model any covariate with VIF>8, and further assessing any covariate with a VIF >4.[2] For this latter group, we reviewed correlation to identify those covariates that were highly correlated (with correlation coefficient > 0.80 and eliminated one of the two highly correlated covariates. For any pair of highly correlated covariates, we retained the covariate most similar to previously identified risk factors, or the one most intuitively related to bleeding risk. For example, the covariates “STEMI on presentation” and “Emergent Procedure” were highly correlated (with STEMI VIF>4 and correlation coefficient of 0.834). We chose to eliminate STEMI and retain “Emergent Procedure”, as the latter was less correlated with other included variables (including NSTEMI on presentation).

In addition to guarding against co-linearity of covariates, the number of variables were limited to prevent potential instability in the propensity model through the inclusion of “too many” covariates. While propensity models are generally more resilient to over-fitting than traditional risk prediction models, a general principle of including one covariate for every four or greater outcome events has been recommended.[3] However, we chose to not explore the CathPCI data for rates of adverse outcomes, prior to the development of the propensity model, in an effort to establish a more generalizable approach to prospective, active, surveillance. This approach is consistent with recommended practice for covariate selection for propensity matching methods, whereby using data other than the dataset to be analyzed is preferred.[4] In the absence of having accurate adverse outcome rates to guide the limit of covariates to include in the propensity model, we chose to be conservative in the total number of covariates included in the final propensity model, which influenced our original candidate covariate list.

B.3.c: Adaptation of O'Brien-Fleming Alpha Spending Function for Prospective, Active Surveillance: A widely recognized challenge in the statistical literature is the phenomenon that repeatedly evaluating accumulating data can increase the rate of incorrectly declaring outcome significance, a term frequently described as "alpha error inflation."[5,6] To reduce the risk of this error, alpha-spending methods, such as the O'Brien-Fleming method were developed to provide statistically valid inferences from accruing datasets in traditional randomized clinical trials.

While not a prospective randomized trial, the design of the primary analysis in this study was pre-specified by protocol, and fulfills all of the statistical requirements for use of these methods. These requirements include 1) pre-specification of the use of an alpha spending function, 2) determination of information fraction as a function of the total calendar time of the analyses, and 3) use of 1:1 propensity score matching, which results in equal numbers of subjects in each treatment group at all interim analyses. Given that the study design had satisfied these three criteria, we adapted the O'Brien-Fleming method to apply to pre-specified, active surveillance, in order to reduce the chance of Type I error during active surveillance. Importantly, the O'Brien-Fleming method spends most of the alpha in the ending time period and prevents early alerts which is beneficial within active surveillance to minimize early, voluminous alerting when the volume of information is low relative to the desired final analysis.

B.4 Additional Post-hoc Exploratory Analyses:

In light of the findings of the study, the Steering Committee requested several additional post-hoc, and therefore exploratory, analyses be performed to further understand the safety signals associated with Mynx VCD use.

B.4.a: Mynx VCD Use Over Time: As shown in the Figure S3, Mynx utilization following femoral access for PCI has slowly increased since the end of 2012, with approximately 8,500 implants per quarter (2,800 per month) in the most recent data captured within the CathPCI Registry.   Similarly, Mynx usage, as a proportion of all VCD deployed following PCI with femoral access has increased slightly in the past 3 years, and most recently represents 14% of all VCD usage for this indication.

B.4.b: Safety Surveillance of other Active VCD: We repeated the vascular closure device analysis using Angioseal, Perclose and Starclose VCD, the three most commonly used VCD in the CathPCI Registry.   For each VCD we performed a new propensity match analysis comparing the device of interest to all other active VCD; thereby mimicking the primary analysis performed exploring the Mynx VCD. The results presented in Table S6 indicate that no other commonly used VCD triggered a DELTA adverse safety alerts. A trend toward a small increased risk of vascular complications for the Angioseal VCD (Relative Risk 1.06; CI: 0.99-1.13, p=0.057) was noted, but did not meet statistical significance.

Importantly, both the Perclose VCD and Starclose VCD were associated with statistically significant reductions in vascular complications and the Perclose VCD was also associated with a reduced risk of bleeding as compared with propensity matched VCD.

B.4.c: Comparison of Mynx VCD and All VCD to Manual or Mechanical Compression: We repeated the primary propensity matched analysis for all active VCD and for Mynx alone, using the primary dataset for PCI cases performed in 2011-2013. The results are presented in Table S7, and indicate neither Mynx nor the total population of active VCD demonstrated an increased risk of vascular complications, access site bleeding or transfusion compared with manual or mechanical compression, following PCI. In fact, Mynx VCD itself was protective, as compared with manual/mechanical compression for the outcomes of vascular complications and transfusion requirements. The analysis of Any VCD (versus manual or mechanical compression) demonstrated significantly improved safety for the VCD treated patients. We believe these results support the overall comparative safety findings of the analysis with their focus on device-device comparisons

C. Supplemental Appendix Figures

Figure S1: Mynx VCD use in PCI procedures performed via the femoral artery from the CathPCI DELTA study.

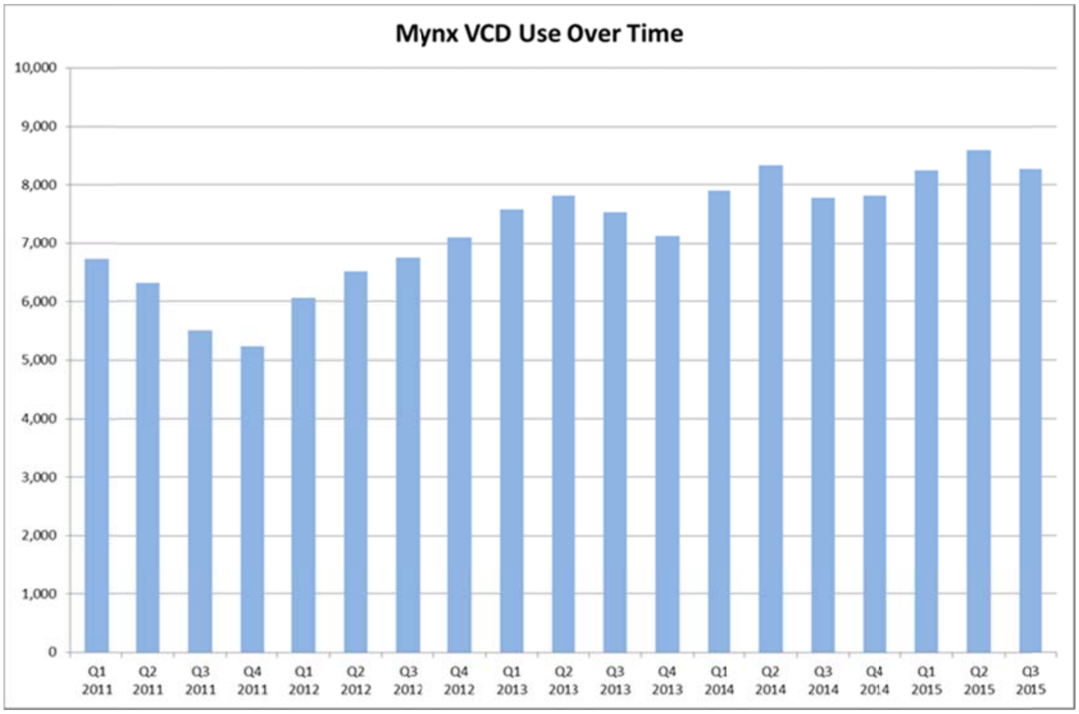
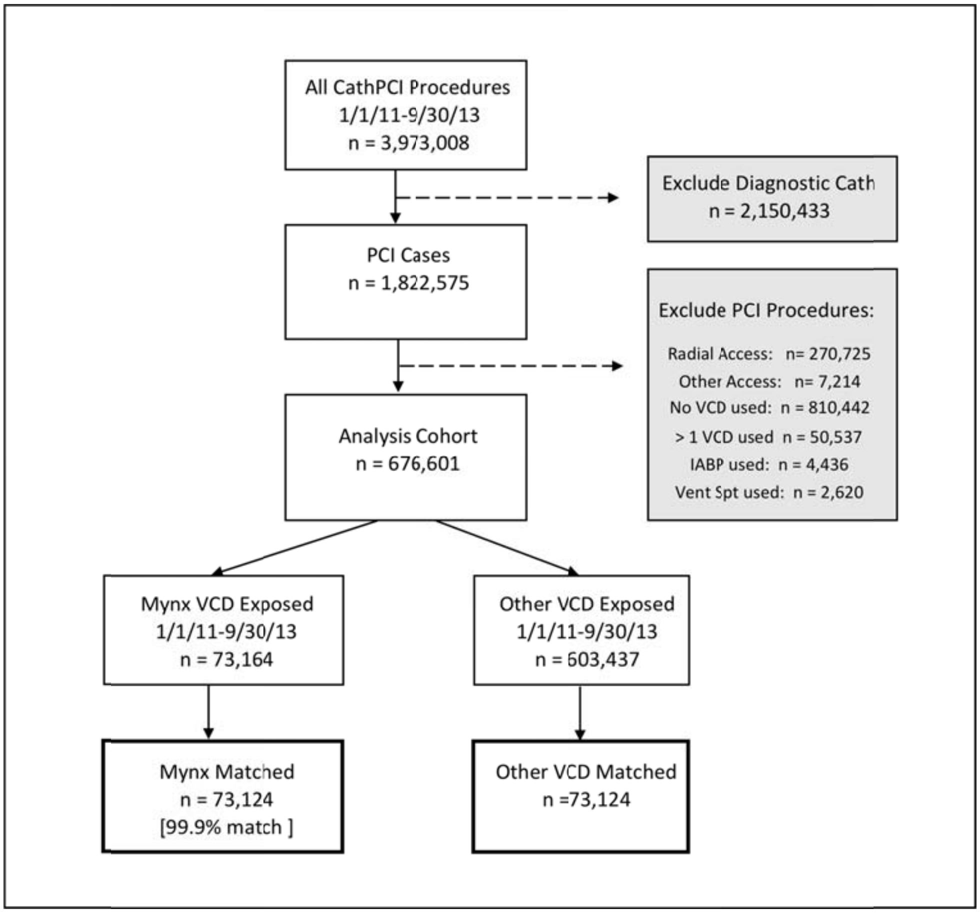
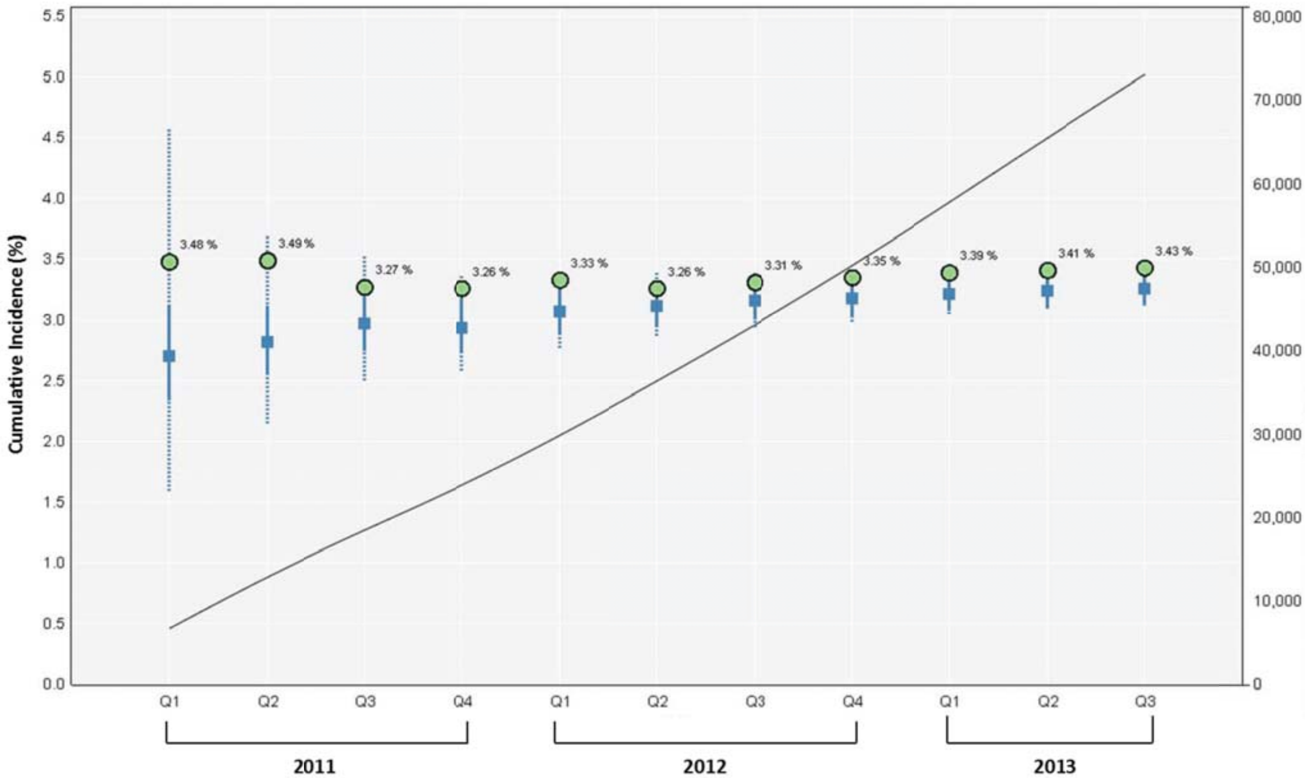


Figure S2: Patient inclusion and exclusion flow for primary analysis cohort (1/1/11 – 9/30/13).



Abbreviations: VCD- denotes vascular closure device; PCI -percutaneous coronary intervention

Figure S3: Post-hoc Falsification Hypothesis: Cumulative Incidence of Development of Post-procedural Contrast Induced Nephropathy (CIN) among Recipients of the Mynx and Alternative VCD (January 1, 2011 – September 30, 2013).



Shown is the cumulative incidence of the development of CIN following use of the Mynx vascular closure device after a PCI procedure. CIN was defined as maximal increase of ≥25% or ≥ 0.5 mg/dl in pre-PCI serum creatinine by time of discharge. The circles indicate observed event rates among Mynx-treated patients, with no safety alerts triggered during the surveillance period. The blue squares indicate the observed event rates in the matched alternative-device group. The bluevertical lines indicate 95% confidence intervals, with dashed lines indicating adjustment for multiple comparisons. The solid black line indicates the cumulative sample size, with values shown on the right vertical axis.

D. Supplemental Appendix Tables

Table S1: Vascular Closure Device Families: VCD models produced by the same manufacturer were grouped together into "Device Families" if they shared mechanisms of implantation and common implant material/devices. Only VCD which delivered an implanted component to the level of the artery were included as "active VCD" for the purposes of this analysis, and are summarized in Table S1. The study excluded cutaneous patches or temporary sealants in the VCD comparator groups including: Boomerang ClosureWire, Exoseal, FloSeal Matrix, and QuickSeal.

Device	Manufacturer	Family
Angiolink EVS	Angiolink	AngioLink
Angio-Seal	St. Jude Medical	AngioSeal
Angio-Seal Millenium	St. Jude Medical	AngioSeal
Angio-Seal STS	St. Jude Medical	AngioSeal
Angio-Seal STS PLUS	St. Jude Medical	AngioSeal
Angio-Seal VIP	St. Jude Medical	AngioSeal
Angio-seal Evolution	St. Jude Medical	AngioSeal
Arstasis	Arstasis Inc	Axera
Duett Pro Sealing-2210	Vascular Solutions	Duett
Duett Sealing Device	Vascular Solutions	Duett
Femoral Introducer Sheath and Hemostasis Device - FISH	MIR	MIR
Mynx	Access	Mynx
Mynx-M5	Access	Mynx
Mynx Cadence	Access	Mynx
MynxGrip	Access	Mynx
Closer S	Abbott Laboratories	Perclose
Perclose A-T	Abbott Laboratories	Perclose
Perclose ProGlide	Abbott Laboratories	Perclose
Prostar XL 8 Suture	Abbott Laboratories	Perclose - Large
Starclose Vascular Clo Sys	Abbott Laboratories	Starclose
Starclose SE	Abbott Laboratories	Starclose
Sutura Superstitch device	Sutura	Sutura
Techstar	Abbott Laboratories	Techstar
Techstar XL	Abbott Laboratories	Techstar
Vasoseal	Datascope Corp.	Vasoseal
Vasoseal Elite	Datascope Corp.	Vasoseal
VasoSeal ES	Datascope Corp.	Vasoseal
VasoSeal Low Profile	Datascope Corp.	Vasoseal
VasoSeal VHD	Datascope Corp.	Vasoseal
X-Press	X-site Medical	X-site

Table S2: Final Propensity Model for Mynx VCD Analysis:

C-Statistic	0.58		
ChiSquareStatistic	5146.3		
Deviance	458457.3		
LogLikelihood	-229,229		

Covariate	Estimate	Standard Error	p-Value
Age (yrs)	-0.0015	0.0004	0.000
Female Gender	0.1259	0.0085	0.000
Body Mass Index (kg/m^2)			
<21	-0.0139	0.0229	0.543
≥25 and <30	-0.0229	0.012	0.055
≥30	0.0121	0.0119	0.310
Diabetes	0.0797	0.0085	0.000
Chronic Lung Disease	0.1593	0.0109	0.000
Hypertension	0.1581	0.0114	0.000
Creatinine pre-procedure (mg/dL)	0.0233	0.0037	0.000
Peripheral Arterial Disease	0.2305	0.0123	0.000
Emergent Procedure	-0.3906	0.0119	0.000
NSTEMI on Presentation	-0.1194	0.0101	0.000
Bivalirudin exposure	0.1072	0.0084	0.000
Left Main Coronary Artery PCI	-0.063	0.0278	0.023
Number of vessels treated during index PC	0.0247	0.0058	0.000
Fluoroscopy time (min)	-0.0179	0.0005	0.000
Total number of PCI during admission	0.0332	0.0182	0.068
Intercept	-2.1068	0.0342	0.000

Table S3: Missing Data in Primary Analysis Dataset:

	Study Dataset prior to Match		
Covariate	Mynx VCD (n=73,164)	Alternate VCD (n=603,437)	Imputation Rule for Missing Data
Age	0.00%	0.00%	
Female Gender	0.00%	0.00%	
Height (cm)	0.11%	0.17%	171 cm
Weight (kg)	0.05%	0.09%	85 kg
Diabetes	0.06%	0.04%	no
Chronic Lung Disease	0.08%	0.04%	no
Hypertension	0.04%	0.03%	no
Creatinine pre-procedure (mg/dL)	4.29%	4.86%	1.04
Peripheral Arterial Disease	0.07%	0.04%	no
Emergent	0.00%	0.00%	
NSTEMI on Presentation	0.00%	0.00%	
Bivalirudin exposure	0.00%	0.00%	
Left Main Coronary Artery PCI	0.00%	0.00%	
Number of vessels treated during index P(	0.00%	0.00%	
Fluoroscopy time (min)	1.00%	1.12%	11.15
Total number of PCI during admission	0.00%	0.00%	

Table S4: Summary of Logistic Regression risk adjustment, Pre-Specified Sensitivity Analysis:

	Mynx VCD - Observed		Predicted Event Rate (%)	Observed/ Expected	Confidence Interval	p-value	Absolute Risk Difference (%)	Time to Alert (Months)
Alternative Risk Adjustment: LR								
Patients	66,429							
Vascular complications	784	1.18%	0.80%	1.48	(1.32-1.67)	<0.001	0.38%	12
Access-Site Bleeding	245	0.37%	0.26%	1.41	(1.14-1.74)	<0.001	0.11%	27
Blood Transfusion	1,210	1.82%	1.53%	1.19	(1.09-1.30)	<0.001	0.29%	15

Table S5: Signal Persistence Analysis

Cohort Analyzed	Mynx VCD		Alternative VCD		Relative Risk	(95% CI)	p-value	Absolute Risk Difference (%)	Time to Alert (Months)
All Patients: 2014-2015									
Patients	48,992		48,992						
Vascular complications	704	1.44%	472	0.96%	1.49	(1.32-1.68)	<0.001	0.47%	6
Access-Site Bleeding	355	0.72%	248	0.51%	1.43	(1.21-1.69)	<0.001	0.22%	12
Blood Transfusion	725	1.48%	614	1.25%	1.18	(1.06-1.32)	<0.001	0.23%	12
High Risk Patient Subsets:									
70 Years or Greater									
Patients	18,914		18,914						
Vascular complications	342	1.81%	229	1.21%	1.49	(1.26-1.78)	<0.001	0.60%	12
Access-Site Bleeding	170	0.90%	111	0.59%	1.53	(1.19-1.96)	<0.001	0.31%	12
Blood Transfusion	429	2.27%	327	1.73%	1.31	(1.13-1.52)	<0.001	0.54%	12
Diabetes									
Patients	20,932		20,932						
Vascular complications	271	1.29%	175	0.84%	1.55	(1.27-1.89)	<0.001	0.46%	12
Access-Site Bleeding	133	0.64%	101	0.48%	1.32	(1.01-1.72)	0.072	0.15%	18
Blood Transfusion	400	1.91%	318	1.52%	1.26	(1.08-1.47)	0.004	0.39%	18
Female									
Patients	16,670		16,670						
Access-Site Bleeding	399	2.39%	263	1.58%	1.52	(1.29-1.78)	<0.001	0.82%	6
Significant Bleeding	205	1.23%	135	0.81%	1.52	(1.21-1.90)	<0.001	0.42%	12
Blood Transfusion	423	2.54%	338	2.03%	1.25	(1.08-1.45)	0.0037	0.51%	15

Table S6: Safety Surveillance of other Active VCD.

Cohort Analyzed	Study VCD		Alternative VCD		Relative Risk	(95% CI)	p-value	Absolute Risk Difference (%)	Time to Alert (Months)
Myxn vs Other VCD									
Patients	73,124		73,124						
Vascular complications	883	1.21%	555	0.76%	1.59	(1.42-1.78)	<0.001	0.45%	9
Access-Site Bleeding	277	0.38%	207	0.28%	1.34	(1.10-1.62)	0.001	0.10%	30
Blood Transfusion	1,328	1.82%	1,080	1.48%	1.23	(1.13-1.34)	<0.001	0.34%	15
Angioseal vs Other VCD									
Patients	275,403		275,403						
Vascular complications	2,273	0.83%	2,147	0.78%	1.06	(0.99-1.13)	0.057	0.05%	n/a
Access-Site Bleeding	784	0.28%	799	0.29%	0.98	(0.88-1.09)	>0.20	-0.01%	n/a
Blood Transfusion	4,070	1.48%	4,315	1.57%	0.94	(0.90-0.99)	>0.20	-0.09%	30*
Perclose vs Other VCD									
Patients	144,162		144,162						
Vascular complications	842	0.58%	1,309	0.91%	0.64	(0.59-0.71)	<0.001	-0.32%	9*
Access-Site Bleeding	365	0.25%	454	0.31%	0.80	(0.69-0.93)	0.002	-0.06%	21*
Blood Transfusion	2,153	1.49%	2,242	1.56%	0.96	(0.90-1.02)	0.176	-0.06%	n/a
Starclose vs Other VCD									
Patients	43,104		43,104						
Vascular complications	257	0.60%	327	0.76%	0.79	(0.66-0.94)	0.004	-0.16%	30*
Access-Site Bleeding	102	0.24%	110	0.26%	0.93	(0.69-1.24)	>0.20	-0.02%	n/a
Blood Transfusion	580	1.35%	610	1.42%	0.95	(0.84-1.07)	>0.20	-0.07%	n/a

* denotes DELTA alert for statistically significant safety benefit relative to Alternative VCD

Table S7: Comparing Mynx (and other VCD) to Manual and Mechanical Compression

Cohort Analyzed	Study VCD (%)		Manual/Mechanical (%)		Relative Risk	(95% CI)	p-value	Absolute Risk Difference (%)	Time to Alert (Months)
Myxn vs Manual/Mechanical									
Patients	73,113		73,113						
Vascular complications	883	1.21%	1,010	1.38%	0.87	(0.79-0.96)	0.003	-0.17%	30*
Access-Site Bleeding	278	0.38%	349	0.48%	0.80	(0.67-0.94)	0.099	-0.10%	30*
Blood Transfusion	1,328	1.82%	1,538	2.10%	0.86	(0.80-0.93)	<0.001	-0.29%	18*
Any VCD vs Manual/Mechanical									
Patients	526,745		526,745						
Vascular complications	4,527	0.86%	7,495	1.42%	0.60	(0.58-0.63)	<0.001	-0.56%	6*
Access-Site Bleeding	1,628	0.31%	2,399	0.46%	0.68	(0.63-0.73)	<0.001	-0.15%	9*
Blood Transfusion	8,951	1.70%	12,726	2.42%	0.70	(0.68-0.72)	<0.001	-0.72%	3*

* denotes DELTA alert for statistically significant safety benefit relative to Manual or Mechanical Compression.

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